

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 41/00	A2	(11) International Publication Number: WO 00/41726 (43) International Publication Date: 20 July 2000 (20.07.00)
(21) International Application Number: PCT/US00/00852 (22) International Filing Date: 14 January 2000 (14.01.00) (30) Priority Data: 60/116,235 15 January 1999 (15.01.99) US (71) Applicant (for all designated States except US): LIGHT SCI-ENCES, LTD. [US/US]; No.E-5, 1065 12th Avenue N.W., Issaquah, WA 98027 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): CHEN, James [US/US]; 2011 - 87th Place N.E., Bellevue, WA 98004 (US). (74) Agents: MAYS, Thomas, D. et al.; Morrison & Foerster LLP, 2000 Pennsylvania Avenue N.W., Washington, DC 20006-1888 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: NONINVASIVE VASCULAR THERAPY (57) Abstract The present invention is drawn to methods and compounds for transcutaneous photodynamic therapy ("PDT") of a target tissue or compositions in a mammalian subject, which includes administering to the subject a therapeutically effective amount of a photosensitizing agent or a photosensitizing agent delivery system or a prodrug, where the photosensitizing agent or photosensitizing agent delivery system or prodrug selectively binds to the target tissue; and irradiating at least a portion of the subject with light at a wavelength absorbed by the photosensitizing agent or if prodrug, by a prodrug product thereof, where the light is provided by a light source, and where the irradiation is at low fluence rate that results in the activation of the photosensitizing agent or prodrug product. These methods of transcutaneous PDT are useful in the treatment of specifically selected target tissues, such as: vascular endothelial tissue; abnormal vascular wall of tumors; tumors of the head and neck; tumors of the gastrointestinal tract; tumors of the liver; tumors of the esophopharyngeal; tumors of the lung; lymphoid tissue; lesions in the vascular system; bone marrow and tissue related to autoimmune disease.		

NONINVASIVE VASCULAR THERAPY

TECHNICAL FIELD OF THE INVENTION

This invention relates generally to the field of medicine and
5 pharmacotherapeutics with photosensitizing agents or other energy activated agents.
Specifically, this invention relates to methods, compounds, compositions and kits
useful for site specific delivery to a lesion target site of a therapeutically effective
amount of a photosensitizing agent that is activated by a relatively low fluence rate of
light over a prolonged period of time. This invention further relates to the use of
10 either an external or internal light source effective in providing transcutaneous
photodynamic therapy as a treatment modality for atherosclerotic lesions and
restenotic lesions in vivo.

BACKGROUND OF THE INVENTION

15 One form of energy activated therapy is photodynamic therapy (PDT). PDT
has been applied to the vascular system to treat atherosclerotic lesions and restenotic
lesions in vivo.

PDT is performed by first administering a photosensitive compound
systemically or topically, followed by illumination of the treatment site at a
20 wavelength or waveband which closely matches the absorption spectra of the
photosensitizer. In doing so, singlet oxygen and other reactive species are generated
leading to a number of biological effects resulting in cytotoxicity. The depth and
volume of the cytotoxic effect in tissue depends on the complex interactions of light
penetration in tissue, the photosensitizer concentration and cellular location, and
25 availability of molecular oxygen.

Vascular lesions are typically treated by light delivered from within the vessel
by a fiberoptic probe as described by Mackie *et al* (Lasers in Surgery and Medicine
11:535-544 (Wiley-Liss, Inc. 1991). Since light is delivered from within the lumen of
the vessel, the vessel by necessity must be punctured in order to introduce the optical
30 fiber. Puncture of an arterial vessel is associated with various medical risks including,
downstream embolization from intravascular dislodgement of plaque or other debris;
bleeding of the puncture site at the skin or vessel; heparinization may cause bleeding
or other side effects; intimal flap from passage of the optical fiber causing

5,829,448). The two-photon methodology requires a high power laser for drug activation with a highly collimated beam that requires a high degree of spatial control. For a large tumor this treatment is not practical since the beam would have to be swept across the skin surface in some sort of set, repeatable pattern over time. Patient or organ movement would be a problem, because the beam could become misaligned. Non-target tissue or skin and subcutaneous tissue photosensitivity is not addressed in the literature available. Any sensitizer in the path of the beam would be activated and cause unwanted collateral tissue damage. The present disclosure is a one-photon method and therefore teaches away from the two-photon method. Further, the present invention teaches and enables the prolonged exposure at a lower fluence rate, which promotes the protection of non-target tissue or skin and subcutaneous normal tissue and reduces collateral tissue damage.

Other modalities have employed the use of low total fluence of PDT delivered over a short time period to avoid skin photoactivation and the use of drug administration timing methods to enable destruction of small tumors in animals (see: U.S. Patent 5,705,518 (Richter *et al.*). However, the present disclosure teaches away from this method in order to enable large total fluence PDT, but at a lower fluence rate, which enables the treatment of larger tumor volumes. Richter *et al.* further fails to teach or disclose the suggestion of a targeting scheme as presently disclosed.

In the event that the target lesion lies below an intact cutaneous layer, the main drawbacks of all transcutaneous illumination methods, whether they be external laser or external nonlaser light sources, are: 1) the risk of damage to non-target tissues, such as the more superficial cutaneous and subcutaneous tissues overlying the target lesion, 2) limitation of treatment volume, and 3) limitation of treatment depth. Damage to normal tissue between the light source and the target occurs due to the uptake of photosensitizer by the skin and other tissues overlying the lesion with resultant unwanted photoactivation in these tissues. The consequences of inadvertent skin damage caused by transcutaneous light delivery to a subcutaneous lesion may include severe pain, serious infection, and fistula formation. The limited volume of a target lesion that can be clinically treated and the limitations of the light penetration below the skin surface in turn have limited clinical transcutaneous PDT to superficial, thin lesions.

utilized for longer than about 2 hours to increase photoactivation depth. This teaches away from the use of a high powered, brief exposure using collimated light as disclosed in W.G. Fisher, *et al.*, *Photochemistry and Photobiology*, 66(2):141-155, 1997.

Clearly, there is a need to improve the method of transcutaneous PDT to enable the safe and practical application of transcutaneous light to vascular lesions in large and small blood vessels without risking damage to non-target tissues, such as skin and normal subcutaneous tissue. The present disclosure teaches a method of photoactivation and photosensitizer construct which improves on the prior art by enabling PDT induced cytotoxicity on both macro- and microscopic scales without risk to the cutaneous layer. Also, the therapeutic index is enhanced due to a specific targeting scheme.

Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein.

20 SUMMARY OF THE INVENTION

The present invention is based on the precise targeting of photosensitive agents or other energy activated agents, drugs and compounds to specific target cells or compositions of a subject or patient and to the method of activation of these targeted photosensitizer agents or other energy activated agents by subsequently administering to the subject light or ultrasonic energy at a relatively low intensity rate and over a prolonged period of time, utilizing a light or ultrasonic energy source that is either external or internal to the target tissues in order to achieve maximal cytotoxicity with minimal side effects.

One embodiment of the present invention is drawn to a method for transcutaneous photodynamic therapy ("PDT") of a vascular lesion in a mammalian subject comprising: administering to the subject a therapeutically effective amount of a photosensitizing agent or a photosensitizing agent delivery system or a prodrug, where the photosensitizing agent or photosensitizing agent delivery system or prodrug

vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated..

A still further embodiment of the present invention is drawn to a method of transcutaneous PDT, where the photosensitizing agent is selected from the group consisting of: indocyanine green (ICG); methylene blue; toluidine blue;
5 aminolevulinic acid (ALA); chlorin compounds; phthalocyanines; porphyrins; purpurins; texaphyrins; and any other agent that absorbs light in a range of 500 nm - 1100 nm. A preferred embodiment of this invention contemplates that the photosensitizing agent is indocyanine green (ICG).

10 One other embodiment of the present invention is drawn to a method of transcutaneous PDT, where the activation of the photosensitizing agent will likely occur within 30 minutes to 72 hours of irradiation, more preferably within 60 minutes to 48 hours of irradiation and most preferably within 3 hours to 24 hours of irradiation. Of course, clinical testing will be required to determine the optimal
15 illumination time. In addition, it is contemplated that the total fluence delivered will preferably be between 30 Joules to 25,000 Joules, more preferably be between 100 Joules and 20,000 Joules, and most preferably be between 500 Joules to 10,000 Joules. Clinical testing will determine the optimal total fluence required to reduce the atheroma and undesirable tissue causing restenotic lesions.

20 A still further embodiment of this invention is drawn to a method for transcutaneous photodynamic therapy of target lesion in a mammalian subject comprising: administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, where the antibody or antibody fragment
25 selectively binds to a target antigen found on thick or thin neointimas, arterial plaques, , vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated. This step is followed by administering to the subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to a photosensitizing agent or
30 photosensitizing agent delivery system or prodrug, where the first member binds to the second member of the ligand-receptor binding pair. A subsequent step includes irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by the photosensitizing agent or if prodrug, by the product thereof. This

underneath the patient's intact skin layer, but is external to the blood vessel to be treated. An additional preferred embodiment of this invention provides that the ultrasonic sensitizing agent is conjugated to a ligand and more preferably, where the ligand is selected from the group consisting of: a target lesion specific antibody; a target lesion specific peptide and a target lesion specific polymer. Other preferred
5
embodiments of the present invention contemplate that the ultrasonic sensitizing agent is selected from the group consisting of: indocyanine green (ICG); methylene blue; toluidine blue; aminolevulinic acid (ALA); chlorin compounds; phthalocyanines; porphyrins; purpurins; texaphyrins; and any other agent that absorbs light in a range
10
of 500 nm -1100 nm. A preferred embodiment of this invention contemplates that the photosensitizing agent is indocyanine green (ICG).

Other embodiments of the present invention are drawn to the presently disclosed methods of transcutaneous PDT, where the light source is positioned in
15
proximity to the target tissue of the subject and is selected from the group consisting of: an LED light source; an electroluminescent light source; an incandescent light source; a cold cathode fluorescent light source; organic polymer light source; and inorganic light source. A preferred embodiment includes the use of an LED light source.

Yet other embodiments of the presently disclosed methods are drawn to use of
20
light of a wavelength that is from about 500 nm to about 1100 nm, preferably greater than about 650 nm and more preferably greater than about 700 nm. A preferable embodiment of the present method is drawn to the use of light that results in a single photon absorption mode by the photosensitizing agent.

Additional embodiments of the present invention include compositions of
25
photosensitizer targeted delivery systems comprising: a photosensitizing agent; and a ligand that binds a receptor on the target tissue with specificity. Preferably, the photosensitizing agent of the targeted delivery system is conjugated to the ligand that binds a receptor on the target lesion with specificity. More preferably, the ligand
30
comprises an antibody that binds to a receptor. Most preferably, the receptor is an antigen on thick or thin neointimas, arterial plaques, , vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated..

A further preferred embodiment of this invention contemplates that the

DETAILED DESCRIPTION OF THE INVENTION

This invention provides methods and compositions for treating a target tissue or destroying or impairing a target cell or composition in a mammalian subject by the specific and selective binding to the target tissue, cell or composition of a
5 photosensitizer agent. This method comprises irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but an overall high total fluence dose results in minimal collateral tissue damage.

Terms as used herein are based upon their art recognized meaning and from
10 the present disclosure should be clearly understood by the ordinary skilled artisan. For sake of clarity, terms may also have particular meaning as would be clear from their use in context. For example, transcutaneous more specifically herein refers to the passage of light through unbroken tissue. Where the tissue layer is skin or dermis, transcutaneous includes transdermal and the light source is external to the outer skin
15 layer. However, where transillumination refers herein to the passage of light through a tissue layer, such as the outer layer of a blood vessel, the light source is external to the blood vessel, but internal or implanted into the subject or patient.

Specifically, the present invention is based on the precise targeting of
20 photosensitive agents or drugs and compounds to specific target antigens of a subject or patient and to the method of activation of targeted photosensitizer agents by subsequently administering to the subject light of a relatively low fluence rate over a prolonged period of time from a light source that is external to the target tissue in order to achieve maximal cytotoxicity or reduction of plaque or abnormal intima with minimal side effects or collateral tissue damage.

25 Further, as used herein "target cells" or "target tissues" are those cells or tissues, respectively, that are intended to be impaired or destroyed by this treatment method. Target cells or target tissues take up the photosensitizing agent; then when sufficient radiation is applied, these cells or tissues are impaired or destroyed. Target cells are those cells in target tissues, which include, but are not limited to: vascular
30 lesions, thick or thin neointimas, arterial plaques, neoplasms, vascular smooth muscle cells and the abnormal extracellular matrix of the site to be treated.. "Non-target cells" are all the cells of an intact animal which are not intended to be impaired or destroyed by the treatment method. These non-target cells include but are not limited to healthy

intensity and duration must be limited to avoid overtreating the animal. Timing with respect to dosing with the photosensitive agent is important, because 1) the administered photosensitive agent requires some time to home in on target cells and 2) the blood level of many photosensitive agents decreases rapidly with time.

5 This invention provides a method of treating an animal, which includes, but is not limited to, humans and other mammals. The term "mammals" or "mammalian subject" also includes farm animals, such as cows, hogs and sheep, as well as pet or sport animals such as horses, dogs and cats.

10 By "intact animal" is meant that the whole, undivided animal is available to be exposed to radiation. No part of the animal is removed for separate radiation, in contrast with photophoresis, in which the animal's blood is circulated outside its body for exposure to radiation. The entire animal need not be exposed to radiation. Only a portion of the intact animal subject may or need be exposed to radiation.

15 "Transcutaneously" is used herein as meaning through the skin of an animal subject.

Briefly, the photosensitizing agent is generally administered to the animal before the animal is subjected to radiation.

20 Preferred photosensitizing agents include, but are not limited to, chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens and pro-drugs such as delta-aminolevulinic acid, which can produce drugs such as protoporphyrin. More preferred are: methylene blue; toluidine blue; texaphyrins; and any other agent that absorbs light in a range of 500 nm -1100 nm. Most preferred is indocyanine green (ICG) (for example, see: WO 92/00106 (Raven *et al.*); WO97/31582 (Abels *et al.*) and Devoisselle *et al.*, *SPIE* 2627:100-108, 1995).

25 The photosensitizing agent is administered locally or systemically. The photosensitizing agent is administered orally or by injection which may be intravenous, subcutaneous, intramuscular or intraperitoneal. The photosensitizing agent also can be administered enterally or topically via patches or implants.

30 The photosensitizing agent also can be conjugated to specific ligands reactive with a target, such as receptor-specific ligands or immunoglobulins or immunospecific portions of immunoglobulins, permitting them to be more concentrated in a desired target cell or microorganism. The photosensitizing agent may be further conjugated to a ligand-receptor binding pair, which includes, but is not

result in significant damage to collateral or non-target tissues. Specifically, the intensity of radiation used to treat the target cell or target tissue is preferably between about 5 and 100 mW/cm.². More preferably, the intensity of radiation is between about 10 and 75 mW/cm.². Most preferably, the intensity of radiation is between about 15 and 50 mW/cm.².

The duration of radiation exposure is preferably between about 30 minutes and 72 hours. More preferably, the duration of radiation exposure is between about 60 minutes and 48 hours. Most preferably, the duration of radiation exposure is between about 2 hours and 24 hours.

The total number of joules delivered to the treatment site is contemplated to lie between 30 J-25,000 J, more preferably between 100 J-20,000 J, and most preferably between 500 J-10,000 J.

Of course, clinical testing will be required to determine the optimal fluence rate and total fluence delivered to the treatment site.

While not wishing to be limited by a theory, the inventor proposes that a photosensitizer agent can be substantially and selectively photoactivated in the target cells and target tissues within a therapeutically reasonable period of time and without excess toxicity or collateral damage to non-target tissues. Thus, there appears to be a therapeutic window bounded by the photosensitizer agent dosage and radiation dosage. The formation of photodegradation products of a photosensitizer agent was used as an indicator of photoactivation. Photoactivation of a photosensitizer agent has been postulated to cause the formation of singlet oxygen, which has a cytotoxic effect.

Additionally, the present invention is drawn to a method for transcutaneous ultrasonic therapy of tumors in a mammalian subject or patient by first administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target antigen of thick or thin neointimas, arterial plaques, , vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated.; and simultaneously or subsequently administering to the subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to an ultrasonic sensitizing agent or ultrasonic sensitizing agent delivery

any ligand-receptor binding pair may be useful provided the ligand-receptor binding pair demonstrate a specificity for the binding by the ligand to the receptor and further provided that the ligand-receptor binding pair permit the creation of a first conjugate comprising a first member of the ligand-receptor binding pair conjugated to an
5 antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target antigen of thick or thin neointimas, arterial plaques, , vascular smooth muscle cells and/or the abnormal extracellular matrix of the site to be treated; and further permit the creation of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to an energy sensitizing or
10 photosensitizing agent or energy sensitizing or photosensitizing agent delivery system or prodrug, and further wherein the first member binds to the second member of the ligand-receptor binding pair.

A preferred embodiment of the present invention is drawn to a method where the photosensitizing agent delivery system includes a liposome delivery system
15 consisting essentially of the photosensitizing agent, however the ordinary skilled artisan would readily understand from the present disclosure that other delivery systems may be used. A still further and preferred embodiment of the present invention contemplates the disclosed method where the photosensitizing agent delivery system utilizes both a liposome delivery system and a photosensitizing agent,
20 where each is separately conjugated to a second member of the ligand-receptor binding pair, and where the first member binds to the second member of the ligand-receptor binding pair, and more preferably where the ligand-receptor binding pair is biotin-streptavidin. This embodiment further contemplates that the photosensitizing agent as well as the photosensitizing agent delivery system may both be specifically
25 targeted through the selective binding to a target tissue antigen by the antibody or antibody fragment of the first member binding pair. Such dual targeting is envisioned to enhance the specificity of uptake and to increase the quantity of uptake.

Having now generally described the invention, the same will be more readily
30 understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

specific therapeutically effective dose using standard clinical practices and procedures.

Similarly, the specific fluence rate and total fluence dose may be routinely determined from the disclosure herein.

5 Additionally, the conjugate above could be further conjugated to an imaging agent such as technetium. Thus, the method could further comprise the steps of performing a nuclear medicine scan and imaging the vascular sites to be treated.

10 B. A targeted antibody-photosensitizer conjugate (APC) is constructed which binds selectively to antigens mainly present on neointimas, arterial plaques and/or vascular smooth muscle cells. This ligand-receptor binding pair or APC is infused intravenously and is taken up in the neointimas, arterial plaques, neoplasms, vascular smooth muscle cells and/or the extracellular matrix. When unbound, APC is eliminated from the body. Internal or external light sources may be used to activate
15 the targeted drug.

Any number of antigens may be selected, provided that the antigen is specific for the neointimas, arterial plaques, neoplasms, vascular smooth muscle cells and/or the abnormal extracellular matrix. Such antigens would be known to those skilled in the art. The selection of a specific photosensitizer agent may be made, provided the
20 photosensitizer agent is activated by a light wavelength of from 500 nm to 1100 nm, and more preferably a wavelength of 650 nm, and most preferably by a wavelength of 700 nm or greater. Such photosensitizer agents as provided in this disclosure are contemplated for use herein.

25 C. The PDT light source is an externally positioned light source directed at the site to be treated. The light source may be a laser diode, light emitting diode or other electroluminescent device. The light source is angled and the light beam is focused to as to direct the light through the skin or membrane of the mammalian subject being treated in a direction lengthwise and parallel to the vessel wall. See Figures 1A and 1B.

30 Alternatively, the light source could comprise a laser diode coupled to an optical fiber which is then aimed at the vessel so as to direct the light along the length of the vessel. See Figure 2. The light source could also comprise a strip of light emitting diodes (LEDs) which are then arrayed on the skin or the membrane

CLAIMS

1. A method for destroying or impairing target cells that comprise a lesion in the vascular system in a mammalian subject comprising:

5 administering to the subject a therapeutically effective amount of a photosensitizing agent, wherein said photosensitizing agent selectively binds to target cells of the lesion;

irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent, wherein said light is provided by a light source that is external to the intact body of the subject; and wherein said irradiation is at a relatively low fluence rate that results in the activation of said photosensitizing agent or said prodrug product

10 wherein said PDT drug is cleared from the skin and subcutaneous tissues of the subject prior to said irradiation.

15 2. A method for destroying or impairing target cells that comprise a lesion in the arterial vascular system in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target cell or target tissue antigen;

20 administering to the subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to a photosensitizing agent or photosensitizing agent delivery system or prodrug, wherein the first member binds to the second member of the ligand-receptor binding pair;

irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent, wherein said light is provided by a light source that is external to the subject; and wherein said irradiation is at a relatively low fluence rate that results in the activation of said photosensitizing agent or prodrug product.

30 3. The method of claim 1 or 2, wherein said light source is selected from the group consisting of one or a plurality of: laser diodes, fiber lasers, LEDs, non-laser light source, cold cathode fluorescent tube, incandescent lights, halogen lights,

12. The method of claim 11, wherein said light results in a single photon absorption mode by the photosensitizing agent.

5 13. The method of claim 9, wherein a complex, comprising said photosensitizing agent conjugated to LDL or VLDL, localizes in the lesion.

14. The method of claim 13, wherein said complex is administered intravenously.

10 15. The method of claim 2, wherein said target tissue antigen is selected from the group consisting of: tumor surface antigen; tumor endothelial antigen; non-tumor endothelial antigen; and tumor vessel wall antigen.

15 16. The method of claim 2, wherein said ligand-receptor binding pair is selected from the group consisting of: biotin-streptavidin; chemokine-chemokine receptor; growth factor-growth factor receptor; and antigen-antibody.

20 17. The method of claim 1 or 2, wherein said photosensitizing agent delivery system comprises a liposome delivery system consisting essentially of the photosensitizing agent.

25 18. The method of claim 1 or 2, wherein said light source is pulse modulated to maximize depth of tissue penetration and minimize heat generation and power consumption.

19. The method of claim 1 or 2, wherein the total fluence of the light used for irradiating is between about 30 Joules/cm² and about 25,000 Joules/cm².

30 20. The method of claim 1 or 2, wherein the total fluence of the light used for irradiating is between about 100 Joules/cm² and about 20,000 Joules/cm².

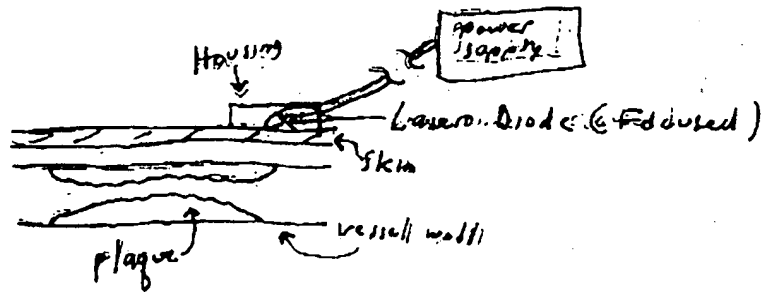


Figure 1A

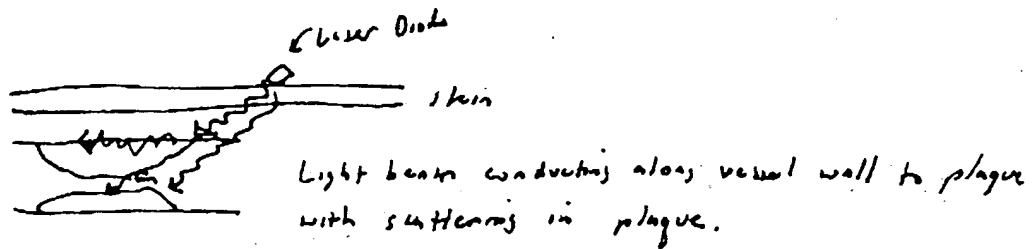


Figure 1B

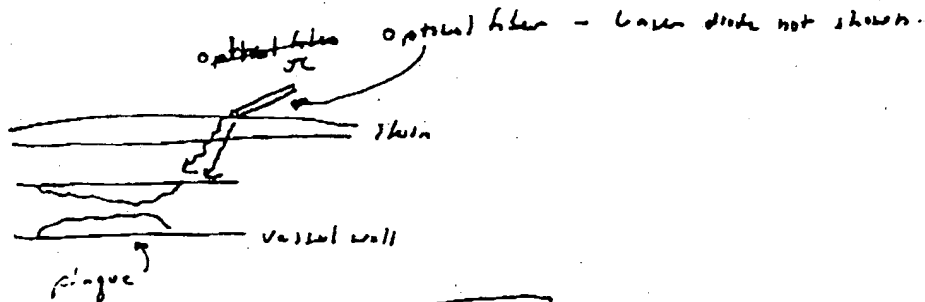


Figure 2